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(54) **Substituted bicyclo (2,2,1)heptanes and hept-2-enes and their pharmaceutical compositions.**

(57) Novel bicyclo [2,2,1] heptanes and hept-2-enes are substituted at the 5-position by a 6-carboxyhex-2-enyl group or a modification thereof, and at the 6-position by a grouping -C(R)-N-NHCO-(NH)$_a$-R' in which R is hydrogen, an aliphatic hydrocarbon residue, an aromatic residue or an aliphatic hydrocarbon residue substituted by an aromatic residue, a is 0 or 1 and R' in an aliphatic hydrocarbon residue, an aromatic residue, or an aliphatic hydrocarbon residue substituted directly or through an oxygen or sulphur atom by an aromatic residue. The compounds are of value for use in pharmaceutical compositions particularly in the context of the inhibition of thromboxane activity.

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This invention relates to biologically active compounds and in particular to certain novel compounds exhibiting activity at thomboxane receptor sites.

Thromboxane A_2 (TXA_2), which is derived from arachidonic acid via prostaglandin H_2 (PGH_2), is implicated in several potentially noxious actions on various body systems, including platelet aggregation, bronchoconstriction and pulmonary and systemic vasoconstriction. Thus TXA_2 may be involved in the normal sealing of blood vessels following injury but in addition may contribute to pathological intravascular clotting or thrombosis. Moreover, the constrictor actions of TXA_2 on bronchiolar, pulmonary vascular and systemic vascular smooth muscle may be important in the development of several anaphylactic conditions including bronchial asthma. Ther is also some evidence to implicate PGH_2 and TXA_2 in the genesis of inflammation.

It is an object of the present invention to provide compounds having activity at thromboxane receptor sites, and most especially to provide compounds which are inhibitors of thromboxane activity and are therefore of interest in one or more areas of medical treatment including the treatment of thrombotic disorders, the treatment of anaphylactic disease states, and treatments utilising anti-inflammatory agents.

Accordingly the present invention comprises a compound being a bicyclo $[2,2,1]$ heptane or hept-2Z-ene which is substituted at the 5-position by a 6-carboxyhex-2-enyl group or a modification

thereof as defined herein, and at the 6-position by a grouping $-C(R)=N-NHCO-(NH)_a-R'$ in which R is hydrogen, an aliphatic hydrocarbon residue, an aromatic residue or an aliphatic hydrocarbon residue substituted by an aromatic residue, a is 0 or 1 and R' is an aliphatic hydrocarbon residue, an aromatic residue, or an aliphatic hydrocarbon residue substituted directly or through an oxygen or sulphur atom by an aromatic residue.

Certain of the compounds containing a modified 6-carboxyhex-2-enyl group act through the conversion of the modified group back to the unmodified group in vivo. In addition to such bioprecursors, the invention also extends in general to other pharmaceutically acceptable bioprecursors for the bicyclo [2,2,1] heptanes and hept-2Z-enes described above, such a bioprecursor being a compound having a structural formula different from the active compound but which upon administration is converted thereto in vivo.

Modifications of the 6-carboxyhex-2-enyl group which may be made in compounds according to the present invention are of two types. Firstly, there are modifications which involve alteration of the hex-2-enyl group by one, or where appropriate by a combination, of the following: (a) reduction of the double bond optionally accompanied by the replacement of a carbon atom at the 5,6 or even the 7 position relative to the C_1 of the carboxylic acid group by a sulphur or particularly an oxygen atom; (b) alteration of the position of the double bond, for example to the 4, 5 position; and (c) shortening or lengthening of the carbon

chain, particularly by one or two methylene groups and conveniently at the end of the chain adjacent to the carboxy group.

The second form of modification, which may if desired be combined with a modification of the first type, involves conversion of the carboxy group to a functional derivative including salts thereof. Functional derivatives described in the prostaglandin art are of particular interest, including esters such as alkyl esters, amides such as those containing the group $-CONHSO_2CH_3$ and variants thereon, and salts with various physiologically acceptable cations. Specific examples of salts are those with an alkali metal such as sodium or with quaternary ammonium ions or amines such as tris. As mentioned above, it will be appreciated that many of such compounds are in fact bioprecursors for the corresponding compound containing a carboxy group to which they are converted in vivo.

Groupings substituted at the 6-position in which R is not hydrogen more usually contain organic groups of a similar type to those described below for R', the aliphatic hydrocarbon and aromatic residue groups being of particular interest. Groupings in which R is hydrogen are however of particular interest.

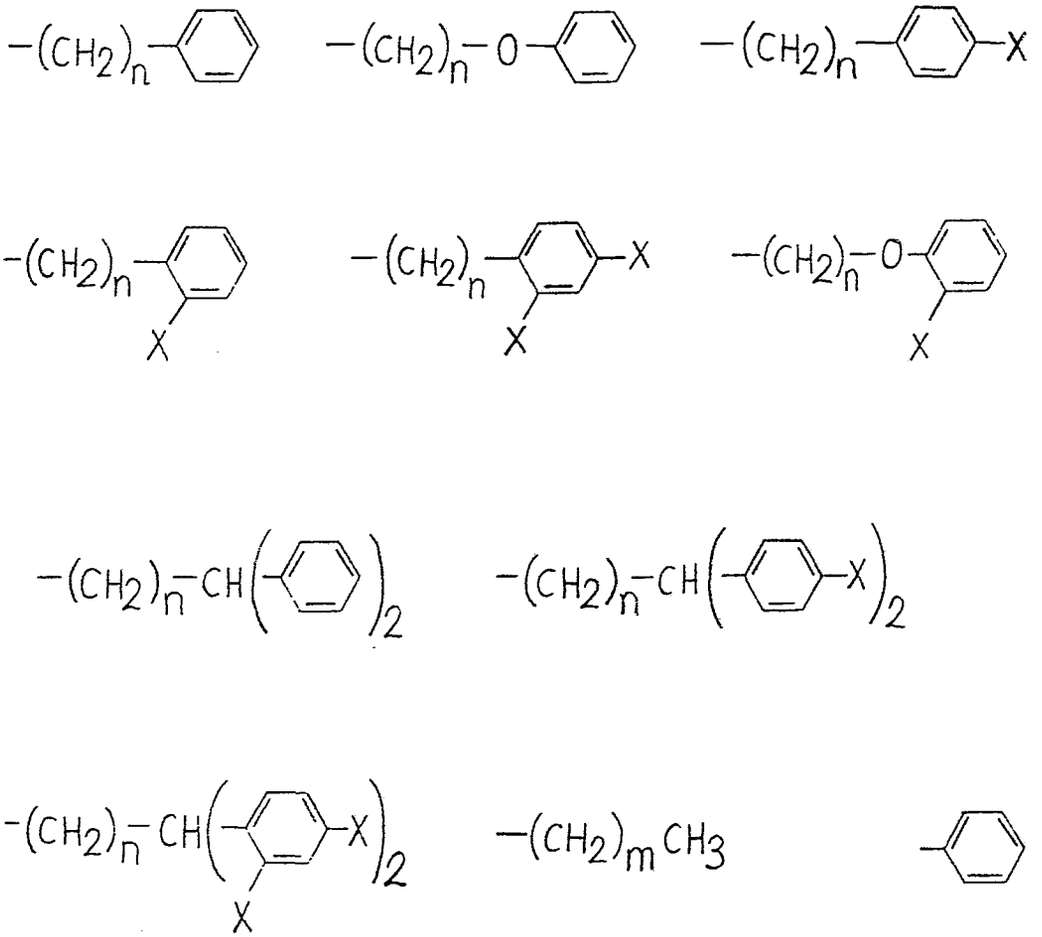
Although the samicarbazone type of grouping, -C(R)=N-NHCO-NH-R', in which a is 1 is of interest, particular interest centres upon the acylhydrazone type of grouping -C(R)=N-NH-CO-R' in which a is 0.

Aliphatic hydrocarbon residues constituting R' may conveniently be of one to five, six, seven, eight, nine, ten or even more carbon atoms, being for example a branched or unbranched alkyl group such as methyl, ethyl, propyl, butyl, amyl, etc. Aromatic residues constituting R' are also of some interest and may be hydrocarbon or heterocyclic residues, which may be unsubstituted or substituted. The heterocyclic residues are more generally linked through a carbon atom so that residues such as pyrid-2-yl, pyrid-3-yl and pyrid-4-yl are of particular interest. Aromatic hydrocarbon residues such as phenyl are, however, of greater interest and these, and also the heterocyclic residues, may be substituted by one or more of various types of group, particularly by substituents being or containing a halogen residue (referred to hereinafter as 'a halogen substituent') for example chloro and especially fluoro, and also halogen substituted alkyl groups such as CF_3, but also other substituents such as sulphonamide groups which may optionally be N-substituted, amino groups which may be free or substituted, for example dimethylamino, hydroxyl groups, methoxy and other higher alkoxy groups containing alkyl groups as described above, etc. Substitution may be present at one or more of the ortho, meta and para positions of a phenyl ring or at a combination of two or more of such positions (including two similar positions), for example at the 2 and 4 positions. The order of interest in the position of substituents depends somewhat on the remaining part of the substituent group R' being

o > m > p in the case of a phenoxyethyl substituent groups R' and o ~ p > m in the case of a benzyl substituent groups R'.

Also of interest, however, are groups R' which are aliphatic hydrocarbon residues substituted directly or through a sulphur or particularly an oxygen atom by an aromatic residue. The aliphatic residues may be of a similar size to those described above but are preferably of three atoms, particular of two atoms and especially of one atom, conveniently being branched or unbranched alkylene groups such as methylene, ethylene or propylene or corresponding trivalent groups of similar size. Similar aromatic hydrocarbon and heterocyclic residues are generally of interest for attachment to the aliphatic residues as have already been described above, the aromatic hydrocarbon residues again generally being of more interest than the heterocyclic residues. Heterocyclic residues, where used, are however of most interest when linked to the aliphatic hydrocarbon residue through the hetero atom such as in pyrid-1-yl. Substitution of an aliphatic hydrocarbon residue particularly terminally, by two or even three aromatic residues and/or substitution through a sulphur or particularly an oxygen atom is of some considerable interest. In case of substitution through sulphur or oxygen, the aliphatic hydrocarbon residue is conveniently of at least two carbon atoms in the case of the semicarbazone type of grouping.

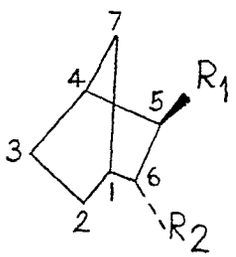
Examples of specific groups R' in both acylhydrazone and semicarbazone types of grouping are:-

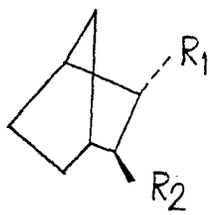


wherein n = 1, 2 or 3, m = 1, 2, 3,4 or 5, and X = Cl, F or CF_3.

It will be appreciated that the structures of the compounds described above provide various opportunities for the occurrence of isomerism although the double bond of the unsaturated ring system is of the Z configuration. The substituents at the 5 and 6

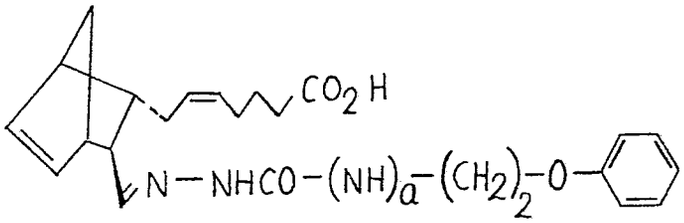
positions of the ring may be in the cis or trans relationship to each other, compounds of the latter configuration being preferred. Moreover, as the ring system is further substituted by a divalent bridging group, then different isomers will exist which vary in which of the 5- and 6- substituents is disposed in a similar direction to the bridging group. Isomers of particular interest are (illustrated for the saturated ring system):

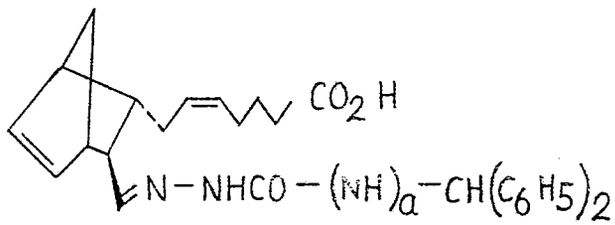




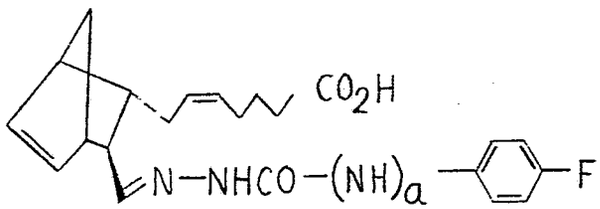
Where the first substituent is a 6-carboxyhex-2-enyl group or a group modified therefrom but still containing the double bond then the configuration about this bond is preferably cis (Z) rather than trans (E). In the second substituent, although syn and anti isomerism is possible about >C=N-double bonds the isomers are often readily interconvertible at room temperature and exist as a mixture which shows biologically activity that may, however, derive predominantly from one isomer. In addition to the foregoing isomerism, the compounds of the present invention will generally be resolvable into enantiomeric forms and one among these may be preferred by virtue of biological activity or physical properties.

Examples of specific compounds according to the present invention are:





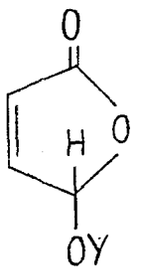
and



and its chloro and trifluoromethyl analogues, as well as the ring saturated analogues of these compounds.

Compounds according to the present invention may conveniently be prepared by using as a starting material a compound containing the unsaturated ring system and having

substituents on the ring system which are suitable precursors for those in the final compound. The formation of such an unsaturated bicyclic ring system is conveniently effected by means of a Diels Alder reaction. Compounds containing the saturated ring system are conveniently produced by reduction of the ring double bond, for example by the use of hydrogen in the presence of a charcoal, such as palladium-charcoal. Such reduction more usually being effected prior to modification of the substituents. A convenient starting material providing suitable precursors for the final substituents is a maleinaldehydic acid pseudo ester of formula



wherein Y represents a hydrocarbon residue, preferably an aliphatic residue such as methyl or especially ethyl. Following reaction of this compound with cyclopentadiene in a Diels Alder reaction, modification of the substituents provided by the ester is effected, conveniently to give initially a 6-carboxy-hex-2-enyl group or a modification thereof and a formyl group, -CHO, which may readily be modified further as desired.

An example of such a procedure is shown in the reaction scheme on page 36 (the numbering of the compounds corresponding to that used in Example 1 and which has also been followed in Example 2 for the ring unsaturated analogue and the following abbreviations are employed in the scheme: Ts, toluene sulphonyl: DMSO, dimethyl sulphoxide; Et, ethyl: Bu, butyl). The use of ethoxycarbonyl rather than methoxycarboyl groups and of ethyl rather than methyl acetal groups has been found to be of value in this procedure. In the final stages of the procedure the acetal group of compound (8) is converted to a formyl group to give compound (9) or compound (9'), and this formyl group is reacted with a suitable reagent or reagents to introduce the appropriate acylhydrazone or semicarbazone type of group, the carboxy group of the 6-carboxy-hex-2-enyl group optionally being protected during this procedure thereby generally giving a slightly greater yield.

The introduction of both types of group may be effected by the action of a suitable reagent either directly with the formyl group in the case of compounds in which R is hydrogen or with the carbonyl group produced through the action of a Grignard reagent on the formyl group (and the subsequent oxidation of the secondary alcohol so formed, for example using the Jones reagent), in the case of compounds in which R is an aliphatic, aromatic or araliphatic residue. The reagent may conveniently take the form of a hydrazide H_2N-NHCOR', or a semicarbazide, H_2N-NHCONHR', respectively. As indicated above, it is possible either to react such a reagent,

for example p-fluorobenzoic acid hydrazide or phenyl semicarbazide, with the compound (9) or with a corresponding compound in which the carboxy group is protected. Such a protected compound is conveniently obtained from the compound (8), for example by reaction with diazomethane followed by treatment with aqueous acid to give compound (9'). Following reaction of the reagent with the formyl group, the carboxy group is deprotected, for example by de-esterification using $KOH/CH_3OH/H_2O$. A similar choice with regard to the nature of the 5-substituent present in the reactant exists when the 6-substituent is a group in which R is other than hydrogen.

Modification of the 6-carboxyhex-2-enyl group may be effected through the initial introduction of a modified group or by modification of this group during or at the end of the sythesis, ester formation conveniently being effected, for example at the stage indicated hereinbefore and amides similarly being prepared by conventional procedures. Indeed, the procedures for effecting the various modifications indicated above will be apparent from the considerable literature existing on prostaglandin chemistry. Thus,for example, one convenient route for the preparation of compounds containing a 6-carboxyhexyl group involves in the case of the bicyclo[2, 2, 1]heptanes a delay in the reduction step used to produce a saturated ring until compound (8) has been obtained when saturation of both the double bond in the ring and that of the 6-carboxyhex-2'2-enyl group may be effected. In the case of the bicycle [2, 2, 1] hept-2Z-enes the corresponding

6-carboxyhexyl-5-formyl compound may be obtained by the Diels Alder reaction of 8-carboxy-1-formyl-oct-1-ene and cyclopentadiene (a separation of the trans isomers obtained being required).

It will be appreciated that the methods described above are not the only ones which may be used for the preparation of compounds according to the present invention and that various alternative procedures may be used as will be apparent to those skilled in the art of prostaglandin chemistry.

It has been found that compounds according to the present invention inhibit the aggregatory activity of 15S-hydroxy-11α-9α(epoxymethano)-prosta-5Z, 13E-dienoic acid [11, 9-(epoxymethano) PGH_2], which is a stable TXA_2 mimic, on human platelets in vitro. It is believed that such inhibition is the result of the compounds being thromboxane antagonists and the activity of the compounds is for convenience hereinafter discussed in these terms. Preferred compounds according to the present invention exhibit a pure antagonist activity. The related compounds described and claimed in our copending application of even date herewith in which the grouping $=N-NHCO-(NH)_a$ in the present compounds is replaced by the grouping =N-O- have been found to show a partial agonist activity in certain tests, such as in the test based on the contractile activity of 11, 9-(epoxymethano) PGH_2 on the rabbit aorta strip, although they are antagonists in the platelet test. Structural features which tend to endow these compounds with a more pure antagonist form of activity are described in that application. It

has been found, however, that the compounds of the present invention generally show little tendency to deviate from pure antagonist activity. Activity has also been observed in compounds according to the present invention on guinea pigs tracheal muscle.

Preferred compounds such as 5-endo(6'-carboxyhex-2'Z-enyl)-6-exo-(N-p-fluorobenzamidoiminomethyl)-bicyclo [2, 2, 1] heptane {5-endo(6'-carboxyhex-2'-Z-enyl)-6-exo-(N-p-fluorobenzamido-carboxaldimine) bicyclo [2, 2, 1] heptane} and 5-endo-(6'-carboxyhex-2'Z-enyl)-6-exo-(N-phenylureido-iminomethyl)-bicyclo [2, 2, 1] heptane {5-endo-(6'-carboxyhex-2'Z-enyl)-6-exo-(N-phenylureido-carboxaldimine)bicyclo [2, 2, 1] heptane} are antagonists in the platelet test, block the aggregatory action of archidonic acid which is converted to TXA_2 by the platelet enzyme system and may or may not block the aggregatory action of ADP which acts via non-TXA_2 sensitive systems. Moreover, they are pure antagonists in the rabbit aorta strip test but do not block the contractile action of noradrenaline which acts on α-adrenoceptors.

Compositions according to the present invention are of interest for the treatment of thrombotic disorders and also for the treatment of anaphylactic disease states, for example as broncho-dilators for the treatment of asthma, etc. They additionally have potential as anti-inflammatory agents. It will be appreciated that the spectrum of activity shown by any particular compound will vary and that certain compounds may be of particular interest in one of these applications whilst other compounds are of particular

interest in another of them. Modifications of a compound can have other advantages. Thus, for example, it has been found that the ring unsaturated compounds described herein are usually less stable than the ring saturated compounds although the latter have similar activity in general. Furthermore the use of esters and other derivatives of the 6-carboxyhex-2-enyl group can have advantages in relation to slow release depot preparation through conversion in vivo to the active compound containing a free carboxy group,, although the low water solubility of the esters must be taken account of.

The compounds may be formulated for use as pharmaceuticals for both animal and particularly human administration by a variety of methods, but usually together with a physiologically acceptable diluent or carrier. The compounds may, for instance, be applied as an aqueous or oily solution or suspension or as an emulsion for parenteral administration, the composition therefore preferably being sterile and pyrogen-free. The preparation of aqueous solutions of compounds in which the 5-substituent terminates in a free carboxy group may be aided by salt formation. The compounds may also be compounded for oral administration in the presence of conventional solid carrier materials such as starch, lactose, dextrin and magnesium stearate. Alternative formulations are as aerosols, suppositories, cachets, and, for localised treatment, as suitable creams or drops. Without comment to a rigid definition of dosage, which is difficult in view of the

different levels of activity, methods of formulation, and methods of administration, some general guidance may be given. In the case of systemic administration to produce a thromboxane antagonism the normal daily dosage which is proposed lies in the range from about 0.1 mg to about 10 mg per kilogram (the average weight of a human being about 70 kg) and particularly from about 1 mg to about 5 mg per kilogram. It will be appreciated, however, that dosages outside this range may be considered, and that the daily dosage may be divided into two or more portions.

The invention is illustrated by the following Examples.

The compounds of the present invention are related to the compounds described and claimed in our copending application of even date herewith in which the grouping $=N-NHCO-(NH)_a-$ in the present compounds is replaced by the grouping $=N-O-$. Further specific examples of variations which may be effected in the common parts of the molecule are to be found in that application. Although the compounds have predominantly the isomeric form indicated, some minor contamination by other isomers, particularly the 5-endo, 6-endo isomer, may be present.

The numbering used for the sub-sections of Example 1 is in accordance with that used in the reaction scheme on page 36 of the specification. In Example 2, sub-sections relating to the analogous ring unsaturated compounds have been similarly numbered.

Example 1: 5-endo-(6'-Carboxyhex-2'Z-enyl)-6-exo-(N-p-fluorobenzamindoimonomethyl)-bicyclo [2, 2, 1] heptane

(1) Maleinaldehydic acid pseudo-ethyl ester

30 g of redistilled furan-2-aldehyde is mixed with 600 ml dry ethanol and 300 mg of methylene blue is added. Dry air is blown gently through the solution and the material is irradiated with a 300 W tungsten lamp for about two days until t.l.c. in a silica gel/ether system shows essentially no remaining starting material. The solution is then stirred with vanadium pentoxide for four hours, filtered, and the solvent removed under reduced pressure. The residual oil is distilled under high vacuum to give the title compound as an oil (23.6g, 76%), b.p. 90 - 92° C/0.2mm

(2) Diels Alder reaction between maleinaldehydic acid pseudo-ethyl ester and cyclopentadiene

Freshly cracked cyclopentadiene (9.0g) is mixed with 11.0g of the pseudo ester (1). A gentle warming is observed and the mixture is allowed to stand overnight. The N.M.R. spectrum typically shows the formation of the adduct (2) to be complete and the material is taken to the next step without purification.

(3) 5-endo-Carboxyethyl-6-exo-diethoxymethyl-bicyclo-[2, 2, 1]-hept-2Z-ene

The Diels-Alder adduct (2) (10 g) is heated in a mixture of triethyl orthoformate (10 ml), dry ethanol (100 ml), and concentrated sulphuric acid (1 ml). The mixture darkens and

after 12 hours is cooled and treated with anhydrous potassium carbonate (5 g) and ether (150 ml). Water is then slowly added with efficient mixing to neutralise the acid. The product is extracted with ether, washed with water and distilled to give the title compound as an oil (7.3g, 63%, b.p. 115 - 120°C/0.3mm.

(4) 5-endo-Carboxyethyl-6-exo-diethoxymethyl-bicyclo[2, 2, 1]-heptane

5-endo-Carboxyethyl-6-exo-diethoxymethyl-bicyclo[2, 2, 1]-hept-2-ene (30 g) is dissolved in 200 ml of ethanol and 0.3 g of 10% palladium on charcoal is added. The mixture is vigorously stirred in 1 atmosphere of hydrogen gas at room temperature. 1 molar equivalent of hydrogen gas is absorbed and the product is then isolated by removal of the catalyst by filtration through a Celite pad, followed by evaporation of the filtrate to give a quantitative yield of the title compound as an oil b.p. 105 - 110°C/1.5 mm.

(5) 5-endo-Hydroxymethyl-6-exo-diethoxymethyl-bicyclo[2, 2, 1]-heptane

The ester (4) (27g) is added in ether to a 10% excess of lithium aluminium hydride (2.1g) in ether with stirring at reflux temperature. The mixture is boiled for 1 hour after the addition and is then quenched by the addition of wet ether followed by 5% aqueous sodium hydroxide to precipitate aluminium salts. The colourless organic phase is dried over magnesium sulphate, filtered and evaporated to give the title compound as an oil (20g, 91%).

(6) 5-endo-Cyanomethyl-6-exo-diethoxy-bicyclo [2, 2, 1] heptane

The alcohol (5) (20g) in a minimum volume of dry pyridine is added slowly to 20g of p-toluenesulphonyl chloride in 130 ml dry pyridine with stirring at 0°C. The mixture is kept at 5°C overnight and then poured into a water-ice mixture. The resulting precipitate is filtered off and dried to give the tosylate ester of the alcohol in 85% yield as an off-white solid, mp 84 - 86°C (dec.).

The tosylate (14g) in 15 ml dimethyl sulphoxide is added to 5g of dry potassium cyanide in 20 ml dimethyl sulphoxide. The mixture is stirred under nitrogen and the temperature slowly raised over 1 hour to 110°C. After 5 hours the reaction mixture is cooled and poured into water. The product is isolated by ether extraction, and purified by distillation to give the title compound (7.8 g, 90%), b.p. 115 - 126°C/1.5 mm.

(7) 6-exo-Diethoxymethyl-bicyclo [2, 2, 1] heptane-5-endo-methyl-carboxaldehyde

The cyano compound (6) (20 g) is stirred at -15°C in 200 ml dry toluene under nitrogen. Di-isobutylaluminium hydride (113 ml of a 1M solution in hexane) is added to the substrate over 25 minutes and the mixture allowed to reach room temperature. After 1 hour, methanol (30 ml) is cautiously added, followed by 400 ml of saturated aqueous sodium hydrogen tartrate. The mixture is stirred and heated at 40°C for 2 hours. The upper organic layer is separated and the aqueous phase further extracted with ethyl

acetate. The combined organic solutions are dried (Mg SO_4) and the solvent removed to give a yellow oil. This is chromatographed on Florisil in benzene to give the pure title compound as a colourless oil (17.2g, 85%) (film): 1725 cm^{-1}

(8) 5-endo-(6'-Carboxyhex-2'Z-enyl)-6-exo-diethoxymethyl-bicyclo [2, 2, 1] heptane

(4-carboxy-n-butyl)-triphenylphosphonium bromide (23.3g) is dried at 75°C under vacuum for 2.5 hours. The resulting white solid is then cooled, the vacuum released to dry nitrogen, and 30 ml of dimethyl sulphoxide is added. A 2M solution of dimesyl sodium in dimethyl sulphoxide (50 ml) is added slowly while the mixture is maintained at 25°C with a water bath. After 15 minutes the aldehyde (7) (5.0g) is added to the deep red ylide thus produced. The mixture is stirred overnight and then the solvent is removed at 55-60°C under vacuum. The residue is dissolved in water, and the aqueous phase is extracted with ether and then carefully acidified to pH4 with 2N HCl. The precipitate is extracted into ether and the ethereal solution is dried and concentrated to give the title compound as an oil(3.7g, 55%).

(9) 5-endo-(6'-Carboxyhex-2'Z-eny)-6-exo-formyl-bicyclo [2, 2, 1] heptane

The acid acetal (8) (1.8g) is dissolved in 200 ml chloroform and 50 ml of concentrated hydrochloric acid is added to form a two phase system. The mixture is vigorously stirred for 90 minutes and is then extracted with ether and the ethereal solution

dried and concentrated. The residual oil is purified by silicic acid chromatography, the oil being applied to the column (prepared by slurrying 10g of Unisil silicic acid - Clarkson Chemical Co., USA - in hexane and pouring into a glass chromatography column) in hexane and elution being carried out with increasing proportions of diethyl ether in hexane up to pure diethyl ether. The chromatography gives the title compound as a colourless oil (1.4g, 83%), υ(film): 757,1715 (broad), 2700 cm^{-1}; δ(90 mHz, $CDCl_3$) 1.2 to 2.6 (18H,m), 5.4 (2H,m), 9.6 (1H,d).

Note: Care should be taken to avoid contact of this compound with methanol since it very readily forms a dimethyl acetal.

(10) 5-endo-(6'-Carboxyhex-2'Z-enyl)-6-exo-(N-p-fluorobenzamido)-iminomethyl)-bicyclo [2, 2, 1] heptane

The aldehyde acid (9) (100 mg) is heated with p-fluorobenzoic acid hydrazide (40 mg) in tetrahydrofuran (5 ml) for 1.5 hours at 40°C. The solvent is then evaporated and the residual oil is purified by silicic acid chromatography, the oil being applied to the column (which is prepared by slurrying 10g of Unisil silicic acid - Clarkson Chemical Co., USA - in hexane and pouring into a glass chromatography column) in hexane and elution being carried out with increasing proportions of diethyl ether in hexane up to pure diethyl ether. The chromatography gives the title compound as an oil (27 mg) which is not readily soluble in ether, λ_{max}(CH_3OH) 254 nm, ε_{max} 12,350. The methyl ester trimethylsilyl ether derivative runs as a single peak on gas chromatography mass spectroscopy and has M^+ 472.

The p-fluorobenzoic acid hydrazide is prepared as follows. Ethyl p-fluorobenzoate (8.4 g) is refluxed with hydrazine hydrate (3.75 g) for 3 hours. The mixture is then cooled, ether is added and the precipitate of p-fluorobenzoic acid hydrazide (3.2 g) is removed by filtration, washed with ether and desiccated, m.p. 149 - 151°C.

Example 2: 5-endo-(6'-Carboxyhex-2'Z-enyl)-6-exo-(N-p-fluoro-benzamido-iminomethyl)-bicyclo[2, 2, 1]hept-2Z-ene

(1), (2), (3) 5-endo-carboxyethyl-6-exo-diethoxymethyl-bicyclo-[2, 2, 1]-hept-2Z-ene

Maleinaldehydic acid pseudo-ethyl ester is prepared as described in Example 1 (1) and reacted with cyclopentadiene in a Diels Alder reaction as described in Example 1 (2). The Diels Alder adduct is treated with ethanol under acidic conditions as described in Example 1 (3) to give 5-endo-carboxy-ethyl-6-exo-diethoxymethyl-bicyclo[2,2,1]-hept-2Z-ene (3).

(5) 5-endo-Hydroxymethyl-6-exo-diethoxymethyl-bicyclo[2, 2, 1]hept-2Z-ene

The ester (3) is added in ether to lithium aluminium hydride (10% excess) in ether with stirring at reflux temperature. After the addition, the mixture is boiled for a further 1 hour. The reaction is quenched with wet ether and then 5% aqueous sodium hydroxide to precipitate aluminium. The colourless organic phase is filtered, dried over anhydrous potassium carbonate, and the resulting alcohol (85 - 90% yield) used directly in the next stage.

(6) 5-endo-Cyanomethyl-6-exo-diethoxymethyl-bicyclo [2, 2, 1] hept-2Z-ene

The alcohol (5) (7g) in 15 ml dry pyridine is added slowly at 0°C to p-toluenesulphonyl chloride (7.5g) in pyridine (45 ml). The mixture is kept overnight at 10°C and then quenched by pouring over ice with vigorous shaking. The product is extracted with ether, washed consecutively with water, 0.1 M sodium carbonate and brine, and then dried (K_2CO_3) and the solvent removed to give the tosylate ester of the alcohol as a colourless oil in high yield.

The tosylate ester (12 g) in dimethyl sulphoxide (15 ml) is added with stirring to potassium cyanide (3 g) in dimethyl sulphoxide (20 ml). The mixture is heated to 100°C under nitrogen for 6 hours and is then cooled, poured into water and the product taken into ether. The solvent is removed and the residue distilled to give title compound as an oil (6.6 g, 88%), b.p. 112-124°C/1.8mm.

(7) 6-exo-Diethoxymethyl-bicyclo [2, 2, 1] hept-2Z-en-5-endo-bicyclo [2, 2, 1] hept-2Z-ene

(4-Carboxyl-n-butyl)-triphenylphosphonium bromide (7.0g) is dried at 75°C under vacuum for 90 minutes. The white solid is cooled, the vacuum is released to dry nitrogen and 10 ml of dimethyl sulphoxide (10 ml) is added followed by 15 ml of a 2M solution of dimesyl sodium in dimethyl sulphoxide. The temperature is maintained at 25°C and the aldehyde (6) (1.5g) is added to the deep red ylide solution. After stirring overnight the solvent is

removed at 55-60°C under vacuum. The residue is dissolved in water, extracted with ether, and the aqueous phase carefully acidified to pH 4 with 2N HCl. The mixture is extracted with ether and the ethereal solution dried and concentrated to give the title compound as an oil (1.34g, 66%).

(9') 5-endo-6-Methoxycarbonylhex-2'Z-enyl)-6-exo-formyl-bicyclo [2, 2, 1] hept-2Z-ene

The acid acetal (8) (5g) in ether is treated with excess ethereal diazomethane to form the methyl ester and then the ketal protecting group is removed by dissolving the compound in 215 ml chloroform and adding concentrated hydrochloric acid (55 ml) to form a two-phase system. The mixture is vigorously stirred for 90 minutes, the reaction being followed by g.l.c. to check on completion. The mixture is extracted with ether and the ethereal solution dried and concentrated to give the title compound as an oil (3.38g, 90%).

(10') 5-endo-(6'-Methoxycarbonylhex-2'Z-enyl)-6-exo-(N-p-fluoro-benzamidoiminomethyl-biccyclo [2, 2, 1] hept-2Z-ene

The aldehyde ester (9') (100 mg) is heated with p-fluoro-benzoic acid hydrazide (40 mg) in tetrahydrofuran (5 ml) for 1.5 hours at 40°C. The solvent is then evaporated and the residual oil is purified by silicic acid chromatography, the oil being applied to the column (which is prepared by slurrying 10g of Unisil silicic acid - Clarkson Chemical Co., USA - in hexane and pouring into a glass chromatography column) in hexane

and elution being carried out with increasing proportions of diethyl ether in hexane up to pure diethyl ether. The chromatography gives the title compound as an oil; M.S.

(10) 5-endo-(6'-Carboxyhex-2'Z-enyl)-6-exo-(N-p-fluorobenzamidoiminomethyl)-bicyclo [2,2,1] hept-2Z-ene

Ester cleavage in compound (10') is effected by heating in aqueous methanol with potassium hydroxide (0.1 N) for 3 hours at 40°C. The product is again purified by silicic acid chromatography, using a 10g Unisil silic acid column made up in hexane and eluting with increasing proportions of diethyl ether in hexane up to pure diethyl ether. The chromatography gives the title compound as an oil.

Example 3: 5-endo-(6'-Carboxy-2'Z-enyl)-6-exo-(N-phenylureidoiminomethyl)-bicyclo [2,2,1] heptane

5-endo-(6'-carboxynex-2'Z-exo-formyl-bicyclo [2,2,1] heptane [100 mg; prepared as described in Example 1(9)] is heated with phenyl semicarbazide (80 mg) in tetrahydrofuran for 2 hours at 40°C. The solvent is then evaporated and the residue purified by silicic acid chromatography as described under Example 1 (10) followed by liquid-gel partition chromatography using a 400 x 15 mm column of Sephadex LH20 substituted with Nedox 1114 olefin oxide to 20% w/w and eluting with dichloroethane/hexane/ethanol (100:100:5 v/v/v) containing 0.1% v/v of acetic acid at a flow rate of 12 ml/hour. The chromatography gives the title compound as an oil (64 mg), λ_{max} (CH_3OH) 248 nm, ε_{max} 17,700.

The phenyl semicarbazide is prepared as follows. Ethyl-N-phenyl carbamate (8.25g) is refluxed with hydrazine hydrate (3.75 g) for 3 hours. The mixture is evaporated to dryness and the residue is treated with ether, and the solid phenyl semicarbazide (1.5 g) is filtered off, washed with ether and dessicated, m.p. 122 - 124°C.

Example 4. 5-endo-(6'-Carboxyhex-2'Z-enyl)-6-exo-(N-p-fluorobenzamido-1'-iminoethyl)-bicyclo[2. 2. 1] heptane and 5-endo(6'-carboxyhex-2'Z-enyl)-6-exo-(N-p-fluorobenzamido-α-iminobenzyl)-bicyclo[2.2.1] heptane

A (1) 5-endo(6'-Carboxyhex-2'Z-enyl)-6-exo-(1'-hydroxyethyl) bicyclo[2. 2. 1] heptane

5-endo-(6'-carboxyhex-2'Z-enyl)-6-exo-formyl bicyclo[2.2.1] heptane is prepared as described in Example 1 (9). This aldehyde (250 mg. 1 mmole) is dissolved in dry tetrahydrofuran (10 ml) at 0°C and treated under nitrogen and with stirring over 30 minutes with a 1M solution of methyl magnesium iodide in ether (2 ml). The mixture is stirred under nitrogen overnight whilst it is allowed to come to room temperature. The reaction is then quenched by the addition of dilute aqueous hydrochloric acid and the product is extracted with ether (3x), the ether solution is dried and evaporated to give the title compound as an oil (200 mg). A small sample is treated to form the methyl ester trimethylsilyl ether and on gas chromatography mass spectroscopy on a 3% OV1 column this shows a carbon value of 18.2, a M^- value of 352 and a base peak of 117.

Chromatography on a column of Sephadex LH 20 substituted with Nedox 1114 olefin oxide to 20% w/w (Lipidex) of the bulk of the oily product using a mixture of (all proportions by volume) 100 parts of hexane, 100 parts of 1,2-dichloroethane, 5 parts of ethanol and 0.1% of the total of glacial acetic acid, as eluant yields the two isomeric secondary alcohols differing in the configuration at the newly introduced asymmetric carbon atom ($-\overset{*}{C}HOH.CH_3$). Nmr spectroscopy on these isomeric products in $CDCl_3$ gives the following δ values: First isomer eluted: 7.3 (s. broad, 1H, OH); 5.45 (m., 2H. olefinic H); 3.6 (m-qxd: 1H. $-\underline{C}HOH$). 2.5-1.0 (m;, 21.H. aliphatic H). 1.2 (d, $\underline{CH}_3$ discernible).

Second isomer eluted: 7.8 (s. broad, 1H, OH); 5.4 (m.,2H. olefinic H); 3.55 (m-qxd, 1H-CHOH); 2.5-1.0 (m,18H,aliphatic H); 1.2 (d, $\underline{CH}_3$ discernible).

(2) 5-endo(6'-Carboxyhex-2'Z-enyl)-6-exo-acetyl-bicyclo [2,2.1] heptane

The procedure described under (1) is repeated with 600 mg of the aldehyde to give a mixture of the two isomeric alcohols (500 mg). This mixture is dissolved in pure acetone (15 ml) and the solution is cooled to $0^{\circ}C$. Jones reagent (600 μ l of a solution prepared by dissolving 26.7 g of chromic anhydride in 23 ml of concentrated sulphuric acid and diluting to 100 ml with water, followed by filtration) is added slowly to the cooled solution with vigorous stirring over 15 minutes. After a further

10 minutes stirring at 0°C the mixture is poured into water and the product extracted with ether. The ether solution is dried and evaporated to give the title compound as an oil (about 75% overall yield from formyl compound). G.C.M.S. (3% OVI) on the methyl ester gives a carbon value of 17.15, a M^+ value of 278 and a base peak of 43/137. Nmr spectroscopy in $CDCl_3$ gives the following δ values.

10.0 (s -broad, 1H, COOH); 5.4 (m,2H, olefinic H); 2.8-1.1 (m 21H, aliphatic H); 2.2 (s, CH_3-CO, discernible).

(3) 5-endo-(6'-Carboxyhex-2'Z-enyl)-6-exo-(N-p-fluorobenzamido-1'-iminoethyl)-bicyclo[2,2,1] heptane

The ketone (2) is reacted with p-fluorobenzoic acid hydrazide in dry pyridine according to the procedure described in Example 1 (10) and the reaction mixtures worked up as described therein to give the title compound.

B (1) 5-endo-(6'-Carboxyhex-2'Z-enyl)-6-exo-(α-hydroxybenzyl-bicyclo[2,2,1]heptane

5-endo-(6'-Carboxyhex-2'Z-enyl)-6-exo-formyl-bicyclo[2,2,1] heptane is prepared as described in Example 1(9). This aldehyde (800 mg) is reacted with 2 equivalents of phenyl magnesium bromide in a similar manner to that described above for the reaction with methyl magnesium bromide. The title compound is obtained as a mixture (900 mg) of the two isomeric secondary alcohols differing in the configuration at the newly introduced carbon atom (-$\overset{*}{C}$HOH.C_6H_5). Gas chromatography mass spectroscopy on the methyl ester

trimethylsilyl ether derivative of a small sample of the mixture of alcohols on a 3% OVI phase at 230°C gives a carbon value (equivalent carbon value relative to retention time of methyl esters of straight chain fatty acids) of about 22, the peak being broad due to a partial separation of the isomers, a M^+ value of 414 with a major ion (M-90) at 324 and a base peak of 179 (C_6H_5CH-OTMS). A n.m.r. spectrum of the mixture of alcohols in $CDCl_3$ gives the following δ values: 7.3 (m,5H, aromatic H), 5.4-5.0 (m, 4H, olefinic H), 4.4-4.2 (d, 1H, CHOH), 2.6-1.0 (m, 18H, aliphatic H).

(2) 5-endo(6'-Carboxyhex-2'Z-enyl)-6-exo-benzoyl-bicyclo [2,2,1] heptane

The mixture of the two isomeric alcohols (1) (900 mg) is dissolved in pure acetone (15 ml) and the solution is cooled to 0°C. The solution is then treated with Jones reagent (1 ml, prepared as described above) and oxidation of the alcohol effected according to the procedure described above to give the title compound as an oil. (~75% from formyl compound). G.c.m.s. on the methyl ester derivative of a small sample of the ketone on a 3% OVI phase at 240°C gives a carbon value of 23.65, a M^+ value of 340 with a major ion at 105 ($C_6H_5CO^+$) and a base peak (M-141) at 199. A n.m.r. spectrum of the ketone in $CDCl_3$ gives the following δ values: 8.1-7.9 (m, 2H, ortho aromatic H), 7.6-7.1 (m, 4H, meta and para aromatic H), 5.3 (m, 2H, olefinic H), 2.8-1.1 (m, 18H, aliphatic H) and an i.r. spectrum (film) give ν values as follows: 1730 (sh), 1705, 1675, 1595 and 1575 cm^{-1}.

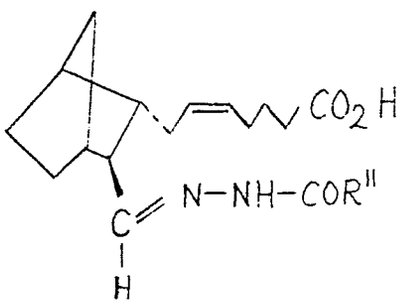
(3) 5-endo(6'-Carboxyhex-2'Z-enyl)-6-exo-(N-p-fluorobenzamido-α-iminobenzyl)-bicyclo[2,2,1]heptane

The ketone(2) is reacted with p-fluorobenzoic acid hydrazide in dry pyridine according to the procedure described in Example 1 (10) and the reaction mixture is worked up as described therein to give the title compound.

Note: In a variation of the procedure described above the reactions with p-fluorobenzoic acid hydrazide in pyridine under (3) is replaced by reaction with phenyl semicarbazide in tetrahydrofuran as described in Example 3 to give the corresponding compounds containing a 6-exo-(N-phenylureido-1'-iminoethyl) or 6-exo-(N-phenylureido-α-iminobenzyl) substituent.

Example 5: 5-endo(6'-Carboxyhex-2'Z-enyl) bicyclo[2,2,1]heptanes containing other 6-exo substituents

The additional compounds of formula

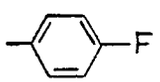
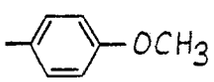
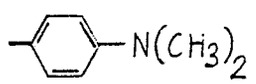
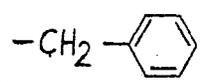
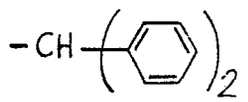
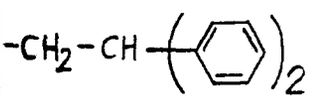
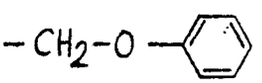
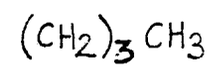
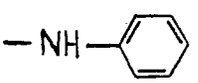


listed in Table 1 below are prepared as described in Example 1 using the appropriate hydrazide. For the purposes of comparison data on the compounds of Examples 1 and 3 has also been included in this table. The free acids may, if desired, be converted to the methyl esters by solution in methanol, using warming and the

addition of $NaHCO_3$ as necessary, followed by the addition of an excess of ethereal diazomethane to the methanolic solution, standing, and the removal of the solvent.

The UV data relates to the main peak(s) of the spectrum in methanol and the MS data relates to values obtained by direct inlet.

Table 1

R''	U.V. Data		M.S. Data
	λ_{max} nm	ε_{max}	M^+
	254	12,350	386
	267.5	22,400	398
	317	23,200	411
	233	14,300	382
	236	13,150	458
	219 235	22,650 15,400	472
	220	16,050	398
	233.5	13,400	348
	248.5	23,500	383

N.m.r. data on the majority of the compounds of Table 1 is presented in Table 2 below. All of the values relate to $CDCl_3$ solution and are referred to $(CH_3)_4$ Si. The term "carbimino proton" is used to identify that proton attached to the carbon atom joined to the 6-position of the ring whilst the term "hydrazono proton" is used to identify the proton of the =N-NH- group.

Table 2

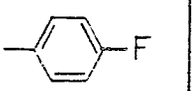
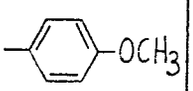
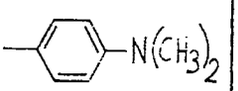
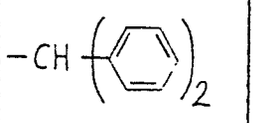
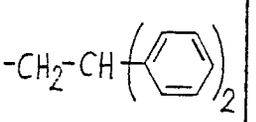
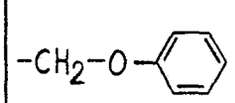
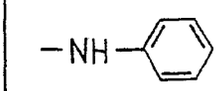
Compound R"	Ethyleric protons in substituent of 5-position of ring	Carbimino proton	Hydrazino proton(1)	Proton in R"
	5.35 (m) 2H	obscured by aromatic H	7.6 (br)1H	7.1(m))4H 7.9(m))
	5.35 (m) 2H	obscured by aromatic H	7.6(br)1H	3.8(s)3H 6.9(m))4H 7.9(m))
	5.35 (m) 2H	7.45(d)1H	6.2(br)1H	3.05(s)6H 6.65(m))4H 7.80(m))
	5.30 (m) 2H	7.2(d)1H	not detected	6.0(s)1H 7.4(m)10H
	5.35 (m) 2H	7.00(d)1H	not detected	3.4(d)2H 4.7(t)1H 7.25(m)10H

Table 2 continued

Compound R"	Ethyleric protons in substituent of 5-position of ring	Carbimino proton	Hydrazino proton(1)	Proton in R"
	5.35(m)2H	obscured by aromatic H	not detected	4.60(s)2H 6.85-7.50(m)4H
	5.40(m)2H	7.15(d)1H	8.8(br)1H	2.7(t)2H 0.95(t)3H
	5.35(m)2H	obscured by aromatic H	8.05(br)1H	9.7(br)1H 7.0-7.6(m)5H

(1) The hydrazino proton is always broad and in some cases the broadening is such that the signal cannot be detected.

Example 6: 5-endo-(6'-Carboxyhexyl)-6-exo-(N-phenylureido-iminomethyl)-bicyclo [2,2,1] heptane

(1) 5-endo-(6'-Carboxyhexyl)-6-exo-formyl-bicyclo [2,2,1] heptane

5-endo-(6'-carboxyhex-2'Z-enyl)-6-exo-diethoxymethyl-bicyclo [2,2,1] heptane is prepared as described in Example 1(8). This acid/acetal (300 mg) is stirred with 10% palladium charcoal (50 mg) in absolute ethanol (10 ml) for 30 minutes whilst continuously passing hydrogen gas through the suspension. The catalyst is removed by filtration through a Whatman No. 50 filter disc and the ethanol is then removed in vacuo. The oily residue

of 5-endo(6'-carboxyhexyl)-6-exo-diethoxymethyl-bicyclo [2,2,1] heptane is dissolved in $CHCl_3$ (50 ml), 2N aqueous hydrochloric acid (50 ml) is added, and the two phase system is stirred for 6 hours at room temperature. Water (100 ml) is then added, followed by diethyl ether (150 ml) and after vigorous shaking the organic phase is separated. The aqueous phase is extracted with a further 150 ml of diethyl ether and the two ether extracts are combined. Evaporation of the diethyl ether from the dried solution gives 5-endo(6'-carboxyhexyl)-6-exo-formyl-bicyclo [2,2,1] heptane as an oil (152 mg), (film) 1715 cm^{-1}(broad); M.S. (methyl ester): M^+/M^++1 266/267 - single peak; δ ($CDCl_3$) 1.1-2.6 (22H, aliphatic H), 9.6 (d, 1H, CHO), 10.0 (broad, COOH).

(2) 5-endo(6'-Carboxyhexyl)-6-exo-(N-phenylureidoiminomethyl)-bicyclo [2.2.1] heptane

The aldehyde/acid (1) (50mg) is reached in tetrahydrofuran with phenyl semicarbazide according to the procedure described in Example 3 and the reaction mixture is worked up according to the procedure described therein to give the title compound as an oil (48mg, 63%, after chromatography), λ_{max} (CH_3OH) 248nm, ε_{max} 15,750; MS (direct inlet on free acid): M^+385.

Example 7: Tests of Biological Acitivity

Various of the compounds described in Examples 1 to 3 are tested for biological activity in the human platelet and rabbit aorta systems.

Human Platelet System

Platelet-rich plasma obtained from fresh, citrated human blood. Addition of the 11,9-epoxymethano analogue of PGH_2 (1×10^{-7} to 5×10^{-7}M) causes immediate aggregation recorded as an increase in light transmission (600 nm). In a second experiment the individual compounds are added 5 minutes previously to addition of the PGH_2 analogue. The dose of the PGH_2 analogue added is then increased to a level which gives a similar response to that obtained in the absence of antagonist. The affinity constant, K_B, for the compound is calculated according to the Gaddum - Schild Equation (based on Law of Mass Action).

$$DR-1 = [B] \times K_B$$

DR = dose ratio

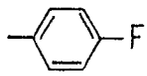
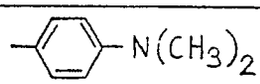
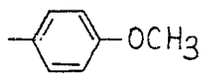
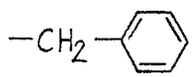
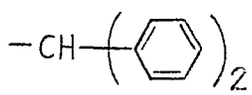
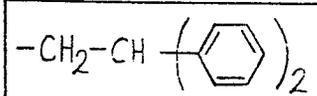
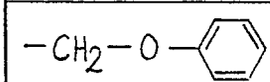
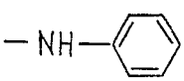
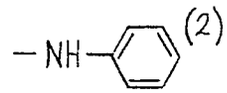
$[B]$ = molar concentration of compound

Rabbit Aorta System

Spiral strips of thoracic aorta are suspended in Kreb's-Henseleit solution and aerated with 95% O_2/5% CO_2 at 37°C. Tension changes are recorded with a Grass FT03 force transducer. Initially, cumulative dose response curves to 11,9-(epoxymethano) PGH_2 (2×10^{-9}, 1×10^{-8}, 5×10^{-8} and 2.5×10^{-7}M) are obtained. In a second experiment the individual compounds are added 30 mins previous to the addition of the series of agonist doses. Affinity constants are calculated as above.

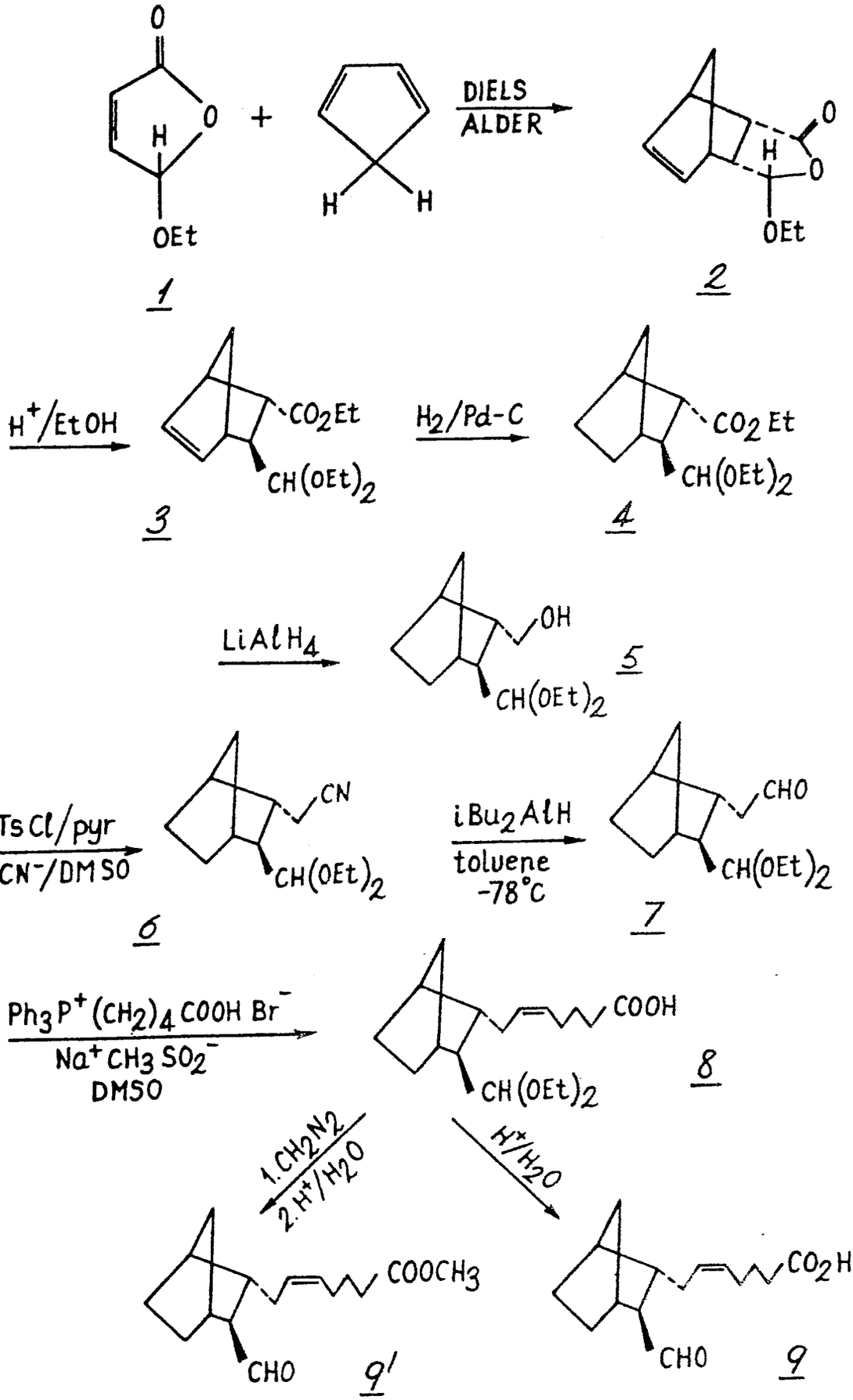
Results typical of those obtained for the various compounds are shown in Table 2. As a standard of comparison, the affinity constant of the potent muscarinic receptor antagonis atrophine is 1 x 10^9 litres/mole.

Table 3

COMPOUND	AFFINITY CONSTANTS x 10^{-5} litres/mole	
	Human Platelets	Rabbit Aorta
	2.1	7.8
	1.0	< 2.5
	-	2.0
	-	6.7
	7.2(1)	39
	20	6.6
	0.52	3.7
	7.0	13
	6.9	8.3

(1) Slight antagonism of ADP; K_B (ADP) = 1.2 x 10^5
The other compounds do not block ADP, having K_B (ADP) of < 0.25 x 10^5.

(2) Double bond in substituent at 5-position is reduced in this compound.


DIELS ALDER
H+/EtOH
H2/Pd-C
LiAlH4
1. TsCl/pyr
2. CN-/DMSO
iBu2AlH
toluene
-78°C
Ph3P+(CH2)4COOH Br-
Na+CH3SO2-
DMSO
1. CH2N2
2. H+/H2O
H+/H2O

CLAIMS

1. A compound being a bicyclo [2,2,1] heptane or hept-2Z-ene which is substituted at the 5-position by a 6-carboxyhex-2-enyl group or a modification thereof as defined herein, and at the 6-position by a grouping $-C(R)=N-NHCO-(NH)_a-R'$ in which R is hydrogen, an aliphatic hydrocarbon residue, an aromatic residue or an aliphatic hydrocarbon residue substituted by an aromatic residue, a is 0 or 1, and R' is an aliphatic hydrocarbon residue, an aromatic residue, or an aliphatic hydrocarbon residue substituted directly or through an oxygen or sulphur atom by an aromatic residue, and pharmaceutically acceptable bioprecursors thereof.

2. A compound according to Claim 1 in which the substituent at the 5-position is a 6-carboxyhex-2-enyl group or a derivative thereof formed at the carboxy group.

3. A compound according to Claim 1, in which the substituent at the 5-position is a 6-carboxyhexyl group or a derivative thereof formed at the carboxy group.

4. A compound according to Claim 1, 2 or 3, in which the 5-substituent terminates in a free carboxy group.

5. A compound according to Claim 1, 2 or 3, in which the 5-substitent terminates in a carboxy group in derivative form.

6. A compound according to Claim 5, in which the derivative is an amide, an ester or a salt of the carboxy group.

7. A compound according to any of Claims 1 to 6, in which R is hydrogen.

8. A compound according to any of the preceding claims in which a is 0.

9. A compound according to any of the preceding claims, in which R' is an aliphatic hydrocarbon or an aromatic residue.

10. A compound according to any of Claims 1 to 8, in which R' is an aliphatic hydrocarbon residue substituted directly or through an oxygen or sulphur atom by a phenyl group or a substituted phenyl group.

11. A compound according to Claim 10, in which the aliphatic hydrocarbon residue is of 1 to 3 carbon atoms.

12. A compound according to Claim 10 or 11, in which the aliphatic hydrocarbon residue is substituted directly or through an oxygen or sulphur atom by a phenyl group or by a phenyl group having one or more substituents selected from alkoxy and amino groups and halogen substituents.

13. A compound according to Claim 12, in which said substituent(s) are chloro, fluoro or trifluoromethyl.

14. A compound according to any of Claims 1 to 8 and 10 to 14 in which R' is an aliphatic hydrocarbon residue substituted by at least two aromatic residues.

15. A compound according to Claim 14 wherein the aliphatic hydrocarbon residue is substituted directly by two phenyl or substituted phenyl groups.

16. A compound according to any of the preceding claims being a bicyclo [2,2,1]-hept-2Z-ene.

17. A compound according to any of the preceding claims being a bicyclo[2,2,1]heptane.

18. A compound according to any of the preceding claims, in which the configuration about any double bond in the 5-substituent is cis.

19. A compound according to any of the preceding claims, in which the 5- and 6-substituents are in trans relationship.

20. A compound according to any of the preceding claims, in which the 5-substituent is oppositely disposed to the bridging methylene group.

21. A pharmaceutical composition comprising a compound according to any of Claims 1 to 20 as an active ingredient thereof in combination with a physiologically acceptable diluent or carrier.

22. A compound according to Claim 1 as described in Example 1, 2, 3, 4, 5 or 6.

European Patent Office

EUROPEAN SEARCH REPORT

0013608

Application number

EP 80 30 0040

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim
A	FR - A - 2 316 926 (SUMITOMO) * Claims * ----	

CLASSIFICATION OF THE APPLICATION (Int. Cl.)

C 07 C 177/00
A 61 K 31/557

TECHNICAL FIELDS SEARCHED (Int. Cl.)

C 07 C 177/00
A 61 K 31/557

CATEGORY OF CITED DOCUMENTS

X: particularly relevant
A: technological background
O: non-written disclosure
P: intermediate document
T: theory or principle underlying the invention
E: conflicting application
D: document cited in the application
L: citation for other reasons

&: member of the same patent family, corresponding document

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
The Hague	26-02-1980	BERTE

EPO Form 1503.1 06.78